Pfizer CentreOne

Making the complex simple for highly potent oral solid dosage forms

Regulatory expectations continue to evolve affecting more than 1,000 small molecule highly potent drug products that are in development as of 2019.[1] The successful production of these drug products is challenged by several factors relative to occupational safety and health during manufacture, as well as downstream, when medications reach patients at the point of care.

To achieve and sustain compliance, pharmaceutical innovators and CMOs must develop a clear understanding of HPOSDs' unique challenges to successfully navigate the complexities of their highly-regulated manufacturing environment. Pfizer CentreOne examines the regulatory considerations for today's HPOSD products.

Defining a HPAPI

Although published guidance defining highly potent active pharmaceutical ingredients (HPAPIs) varies, there is general agreement across the pharmaceutical industry of what characterizes these compounds. For the most part, HPAPIs are defined as an active pharmaceutical ingredient (API) or an intermediate possessing one or more of the following characteristics:

- Biological activity at approximately 150 µg/kg of body weight or below in humans (therapeutic daily dose at or below 10 mg)
- An occupational exposure limit (OEL) at or below 10 µg/m3 of air as an 8-hour time-weighted average
- Sex hormones and certain other steroids
- High selectivity (meaning it can bind to specific receptors or inhibit specific enzymes), with the potential to cause cancer, mutations, developmental defects or reproductive toxicity at low doses
- A novel compound of unknown potency and toxicity. During processing and downstream manufacturing, exposure to these powerful compounds can be hazardous to operating staff, the operating environment, and patients via cross-contamination.

Safety is critical and in the context of HPOSD manufacture is threefold:

1. Safety of operators
2. Safety of product within the quality system
3. Safety from product segregation

Regulators and organizations like the International Council for Harmonisation of Technical Requirement for Pharmaceuticals for Human Use (ICH) have created systems to determine the risks posed by these drugs, along with recommendations for how to manufacture them safely.

Regulatory models evolving for HPOSD manufacturers

The manufacture of HPAPI-based drug products requires appropriate processes plus the expertise and mature quality systems to reduce exposure risk to operators and to prevent cross-contamination.

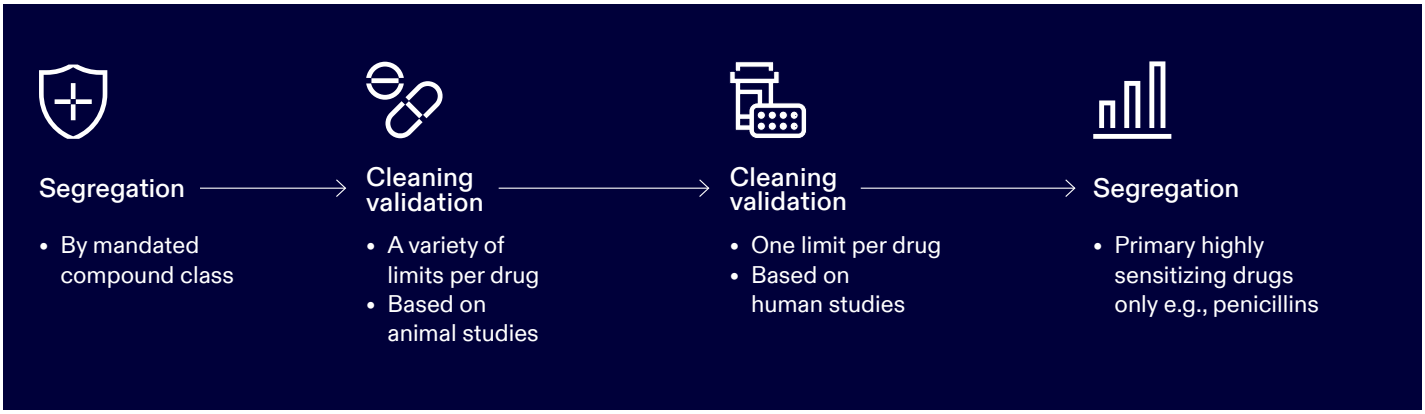
Regulatory authorities in markets around the world all require drug companies to take steps to minimize workers' exposure to HPAPIs through appropriate containment processes. Many established HPAPIs therefore have clearly defined occupational exposure limits (OELs) or occupational exposure bands (OEBs) that all manufacturers must adhere to in order to protect their operators and staff.

While regulators mandate protecting workers and preventing cross-contamination, historically they have never provided well-defined, harmonized standards for how to do it. It is up to manufacturers to determine how to meet regulators' expectations and demonstrate to regulators their methods are sufficient.

To make commercial highly potent drug product manufacturing even more challenging, the regulatory landscape is shifting at a time when pharmaceutical companies and contract companies are responding to increased development activity and ramping up capacity to meet the growing demand for HPOSD therapeutics.

Today, the regulatory environment is simultaneously governed by two main models: the "traditional" model, which has been in play for decades; and a newer, health-based model originated by the European Medicine's Agency (EMA).

The EMA's health-based approach was recently adopted by an international consortium of regulatory bodies, known as the Pharmaceutical Inspection Convention and the Pharmaceutical Inspection Co-operation Scheme (PIC/S). The organization was convened to help harmonize current Good Manufacturing Practice (cGMP) standards around the world.



New approaches to regulatory models

Traditional and health-based models possess striking similarities. Regarding implementation, both offer effective methodologies to achieve containment and sustain compliance. The two models diverge in their approach to segregation and cleaning validation.

Segregation refers to manufacturing drugs in separate facilities or self-contained areas. Originally, segregation was intended to prevent the cross-contamination of highly potent or highly active drugs, though that has largely changed due to advances in cross-contamination control.

Cleaning validation provides cross-contamination control at the equipment level. The goal here is to protect patients and the next batch from being contaminated by compounds made previously in the same equipment.

After manufacturing, equipment is cleaned, and the cleaning process validated to ensure that residues are removed consistently and that there is no risk of carryover. Operation technicians usually assess cleanliness visually before swab samples are taken from inside the equipment or from the liquid used to rinse out manufacturing equipment after it has been cleaned. Depending on specific Pfizer plant quality control, samples are sent for quantitative analysis of any residues remaining on the equipment. Afterwards, operators can check the results to see if any remaining residue exceeds acceptable safety limits.

Pfizer's approach

Pfizer manufactures HPOSD products at several facilities designed specifically to support HPOSD development as well as the safe manufacture and handling of highly potent drug products of many types.

Because these therapeutics are marketed in more than 100 countries, Pfizer's standard operational strategy is to create a safe, consistent, and compliant approach that meets the scrutiny of inspectors from all jurisdictions regardless of the regulatory model they use.

To ensure international compliance, Pfizer takes a dual approach, conforming infrastructure and processes to both the traditional and health-based models. Because the company operates across the regulatory spectrum, when regulatory models shift in a healthbased direction, Pfizer is prepared to move along with them while cooperating with regulators to meet contemporary expectations.

The plant-in-plant concept

Pfizer built the Newbridge, Ireland, plant to meet the segregation requirements of the traditional approach. The company's "plant-in-plant" design appears as one building from the outside, with a single roof covering almost a million square feet. However, lift off that roof and

people will find 10 self-contained areas, each with its own air handling, material flow and personnel flow to achieve complete segregation.

The traditional model mandates segregation by specific compound class. Unfortunately, the point where to "slot" each compound varies among regulators around the world.

At Newbridge, they use a cGMP-proven process to classify each compound based on toxicological information derived from animal and human studies.

The resulting classification dictates whether they should segregate. For drugs that do not require segregation – that is, they can be safely manufactured in a shared area – we conduct a formal quality risk assessment to make sure we have the technical and organizational controls in place to prevent cross-contamination.

Key HPAPI handling considerations

In the manufacture of highly potent drug products, special consideration needs to be given to the technical and organizational controls that will assure both operator safety and control cross-contamination risks to an acceptable level.

While the control strategy for a shared manufacturing facility is multi-factorial, some of the key points to consider in the handling of HPAPI products include the following:

1. Uphold building codes and occupational health and safety standards

It is crucial that the CMO's facility itself has the equipment in place to contain HPAPIs to the area handling them. This infrastructure should include:

- Airlocks around the manufacturing and laboratory spaces, providing gowning and de-gowning facilities for workers accessing or leaving the HPAPI handling area
- Room pressure controls, such as negative pressure in the surrounding rooms to enhance containment to within HPAPI-handling area
- Efficient heating, ventilation and air conditioning systems designed for air-handling unit sharing and filtered recirculation of 100% fresh single pass air
- Safe-change filters inside isolators, ventilated enclosures and general HVAC exhaust system to filter and capture contaminants
- Real-time monitoring to verify the effectiveness of these measures within the main HPAPI-handling area.

2. Ensure the right processes are in place

The latest technology and equipment may be installed in the facility, but if it the purchase is not vetted properly, and proves unsuitable for the specific needs of the site, it will likely be unsuccessful at delivering expected efficiencies or desired results. With this in mind, the following should be considered before specifying and purchasing new equipment or installing an entirely new product line:

- Run risk analyses to identify the unique and specific containment requirements of the site. Following the ISPE's Risk-Based Manufacture of Pharmaceutical Products process (Risk-MaPP) helps ensure that all critical control points are accounted for when installing containment equipment
- Define containment strategies to minimize the remaining contamination risk once equipment has been installed. For instance, 'Clean in Place' requirements for filters and equipment can prevent the release of HPAPIs during essential maintenance of containment equipment
- Institute comprehensive training for those responsible for the handling of HPAPI products to give them the information they need to protect themselves and their colleagues.

Driving your progress in highly potent oral solids

Leveraging the experience of our global network of dedicated colleagues and a team of internal business partners across Pfizer's Global Supply network, Pfizer CentreOne has been consistently recognized for its ability to deliver successful drug programs. As an award-winning CMO, Pfizer CentreOne has been repeatedly recognized for excellence in contract manufacturing, earning multiple CMO Leadership Awards from Outsourced Pharma and Life Science Leader.

Collaboration across sites fosters innovation, helping to ensure medicines reach the patients who need them. Pfizer CentreOne is committed to a culture of confidentiality and complete discretion across all manufacturing facilities and Intellectual Property protection remains a priority for both customers and Pfizer.

Contact Pfizer CentreOne for more information about highly potent oral solids capabilities.

In conclusion

The manufacture of highly potent drug products brings many regulatory challenges related to operator safety and preserving product integrity and quality. However, the application of containment technologies, access to appropriate expertise and comprehensive technical and procedural controls can help ensure the safe and compliant handling of high potency drug products in shared manufacturing facilities.

Selecting the right CMO to deliver a challenging HPOSD project is key to ensuring a safe and ongoing supply of medicines for the patients who need them.

Prestigious legacy. Premium manufacturing.

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References

1. https://www.google.com/url?q=https://www.teknoscienze.com/tks_article/panel-discussion-on-hpapis/&sa=D&source=editors&ust=1742396179179971&usg=AOvVaw1En7sLw7UeFcOpL_aDn58L

PC1-21-0034/March2025-V3

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